

Response to July 6, 2005, Office Action

Atty Dkt No. 03-0185

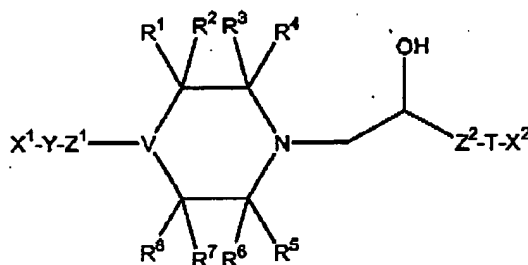
Application No. 10/759,555

AMENDMENTS TO THE CLAIMS

The following listing of claims will replace all prior versions and listing of claims in the application. For the Examiner's convenience a complete listing of all claims incorporating the amendments made herein is attached as Appendix A.

1. (Currently Amended) A compound of Formula I:

wherein:



Formula I

$R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^8 are hydrogen, lower alkyl, or $-C(O)R$;

in which R is $-OR^9$ or $-NR^9R^{10}$, where R^9 and R^{10} are hydrogen or lower alkyl; or R^1 and R^2, R^3 and R^4, R^5 and R^6, R^7 and R^8 , when taken together with the carbon to which they are attached, represent carbonyl; or

R^1 and R^5 , or R^1 and R^7 , or R^3 and R^5 , or R^3 and R^7 , when taken together form a bridging group $-(CR^{12}R^{13})_n-$, in which n is 1, 2 or 3, and R^{12} and R^{13} are independently hydrogen or lower alkyl;

_____ with the proviso that

_____ (a) the maximum number of carbonyl groups is 1;

_____ (b) the maximum number of $-C(O)NR^9R^{10}$ groups is 1; and

_____ (c) the maximum number of bridging groups is 1;

T is oxygen, sulfur, or NR^{11} , in which R^{11} is hydrogen or lower alkyl;

V is $-N<$, $-CH<$, or $-NH-CH<$;

X^1 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

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X² is optionally substituted aryl or optionally substituted heteroaryl;

Y is optionally substituted dihydroheteroaryl; and

Z¹ and Z² are independently optionally substituted alkylene of 1-4 carbon atoms.

2. (Currently Amended) A compound of claim 1, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are independently chosen from hydrogen and methyl and V is -N<.

3. (Original) A compound of claim 2, wherein X¹ is optionally substituted aryl and X² is optionally substituted heteroaryl.

4. (Original) The compound of claim 3, wherein Z¹ is methylene and Z² is methylene or ethylene.

5. (Original) The compound of claim 4, wherein Y is optionally substituted dihydroheteroaryl in which the hetero atoms are chosen from nitrogen and oxygen.

6. (Original) The compound of claim 5, wherein T is oxygen, X¹ is optionally substituted phenyl, and Y is optionally substituted isoxazolyl.

7. (Original) The compound of claim 6, wherein X² is optionally substituted benzothiazolyl.

8. (Original) The compound of claim 7, wherein Y is optionally substituted 5-(4,5-dihydroisoxazol-3-yl).

9. (Original) The compound of claim 8, wherein X¹ is 4-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, and Z² is methylene, namely 1-(2-methylbenzothiazol-5-yloxy)-3-[4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

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10. (Currently Amended) ~~An isomer of the~~ The compound of claim 9, namely (2R)-1-(2-methylbenzothiazol-5-yloxy)-3-[4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

11. (Original) The compound of claim 8, wherein X¹ is 2-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl; R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, and Z² is methylene, namely 3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

12. (Currently Amended) ~~An isomer of the~~ The compound of claim 11, namely (2R)-3-(2-methylbenzothiazol-5-yloxy)-1-[4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]propan-2-ol.

13. (Original) The compound of claim 8, wherein X¹ is 4-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

14. (Currently Amended) ~~The An isomer of the~~ compound of claim 13, namely (2R)-1-[(2S)-2-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

15. (Currently Amended) The compound of claim 8, wherein X¹ is 2-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R³, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R⁷ is (S)-methyl, and Z² is methylene, namely 1-[(3S)-3-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

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16. (Currently Amended) ~~The An isomer of the compound of claim 15, namely~~
(2R)-1-[(3S)-3-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

17. (Currently Amended) The compound of claim 8, wherein X¹ is 4-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R⁷ is (S)-methyl, and Z² is methylene, namely 3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

18. (Currently Amended) ~~The An isomer of a compound of claim 17, namely~~
(2R)-3-[(3S)-3-methyl-4-({5-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-1-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

19. (Original) The compound of claim 8, wherein X¹ is 2-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

20. (Currently Amended) ~~The The isomer of the compound of claim 19, namely~~
(2R)-1-[(2S)-2-methyl-4-({5-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-3-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

21. (Original) The compound of claim 7, wherein Y is optionally substituted 3-(4,5-dihydroisoxazol-5-yl).

22. (Original) The compound of claim 21, wherein X¹ is 4-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, and Z² is methylene, namely 1-[4-({3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl)}methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

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23. (Currently Amended) ~~The An isomer of the compound~~ of claim 22, namely (2R)-1-[4-((5R)-3-[4-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl))methyl]piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

24. (Original) The compound of claim 21, wherein X¹ is 2-(trifluoromethyl)phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, and Z² is methylene, namely 1-[4-((3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl))methyl)piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

25. (Currently Amended) ~~The An isomer of the compound~~ of claim 24, namely (2R)-1-[4-((5R)-3-[2-(trifluoromethyl)phenyl](4,5-dihydroisoxazol-5-yl))methyl]piperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

26. (Currently Amended) The compound of claim 21, wherein X¹ is 4-fluorophenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-(4-(((5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl))methyl))(3S2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

27. (Currently Amended) ~~The An isomer of the compound~~ of claim 26, namely (2R)-1-(4-(((5R)-3-(4-fluorophenyl)(4,5-dihydroisoxazol-5-yl))methyl))(3S2S)-3-methylpiperazinyl)-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

28. (Original) The compound of claim 21, wherein X¹ is phenyl, X² is 2-methylbenzothiazol-5-yl, R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are hydrogen, R³ is (S)-methyl, and Z² is methylene, namely 1-[4-(((5R)-3-phenyl(4,5-dihydroisoxazol-5-yl))methyl)(2S)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

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29. (Currently Amended) ~~The An isomer of the compound~~ of claim 28, namely (2R)-1-{4-[[((5R)-3-phenyl(4,5-dihydroisoxazol-5-yl)methyl](2S)-2-methylpiperazinyl]-3-(2-methylbenzothiazol-5-yloxy)propan-2-ol.

30. (Original) A method of treating a disease state chosen from diabetes, damage to skeletal muscles resulting from trauma or shock and a cardiovascular disease in a mammal by administration of a therapeutically effective dose of a compound of claim 1.

31. (Original) The method of claim 30, wherein the cardiovascular disease is atrial arrhythmia, intermittent claudication, ventricular arrhythmia, Prinzmetal's (variant) angina, stable angina, unstable angina, congestive heart disease, or myocardial infarction.

32. (Currently Amended) The method of claim ~~31~~30, wherein the disease state is diabetes.

33. (Original) A pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of claim 1.